Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2022, 11(4):24-32
https://doi.org/10.51847/IexPv4xRns

Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Regorafenib Adverse Drug Reactions among Patients in King Abdullah Medical City; A Chart Review Study

Hasan Ahmed H Baz[1,2]*, Saeed H. Halawani[3], Ibrahim Abdulaziz[1], Majid Ali[4], Nhal Ahmed Baz[5], Mohammed Jafal[2], Khaldoun Saleh[2]

[1]Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.
[2]Department of Pharmaceutical Care, King Abdullah Medical City, Mecca 24211, Saudi Arabia.
[3]Department of Hematology and Immunology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.
[4]School of Life and Medical Sciences, the University of Hertfordshire (hosted by Global Academic Foundation), Cairo, Egypt.
[5]Department of Periodontist, King Abdullah Medical City, Mecca 24211, Saudi Arabia.

***Email:** Hasbazing5@gmail.com*

ABSTRACT

Regorafenib is widely known as an oral tyrosine kinase inhibitor and antineoplastic agent. It acts on various tyrosine kinase receptors, including oncogenic, stromal, and angiogenic receptors. This study was conducted to determine the safety profile of regorafenib in King Abdullah Medical City. All patients who had received regorafenib in King Abdullah Medical City between December 2021 and May 2020 were included in the study. The data collected included patient demographics, diagnosis, regorafenib starting and escalated doses, reported adverse events, and associated management.
Forty-two patients were found to be on regorafenib. The average age of the patients was 56 years (ranging from 38 to 73 years) of which 12 were females and 30 were males. The majority of the patients received the drug for metastatic colon cancer. The most common adverse event reported in our study was hyperbilirubinemia followed by fatigue. This was in comparison to the adverse events reported in the published literature. Hemifacial spasm and bilateral hydronephrosis were found to be the new adverse drug reactions, which were not reported in other studies. Half of the patients were reported to have discontinued the medication due to adverse events. Regorafenib as evidenced by the published studies and findings of our study was found to be effective in the management of advanced cancers in our local population. However, it was found to be associated with a variety of adverse events comparable to the published studies.

Key words: *Regorafenib, Adverse, Management, Chart review*

INTRODUCTION

Regorafenib is widely known as an oral tyrosine kinase inhibitor and antineoplastic agent. It acts on various tyrosine kinase receptors, including oncogenic, stromal, and angiogenic receptors. Moreover, regorafenib is highly indicated in the treatment of colorectal cancer, especially in metastatic form. It is also indicated for gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma. However, regorafenib has various precautions due to its cytotoxic effects. Therefore, few patients were not suitable to receive regorafenib, including those with severe hepatic impairment (Child-Pugh C), high risk of hemorrhagic events, low white blood cells count, previous cardiac ischemia or infarction, and arterial hypertension [1, 2].

Monitoring adverse drug reactions such as rash, hypertension, and fatigue is beneficial to avoid regorafenib toxicity and helps healthcare practitioners to adjust the regorafenib dose to achieve the best therapeutic results. As mentioned above, regorafenib has many cytotoxic effects which may cause more frequent adverse reactions such as pain, skin rash, diarrhea, infection, and hypertension. It can also cause severe acute adverse reactions such as bleeding, severe liver injury, and gastrointestinal perforation. Furthermore, drug-drug interactions, food-drug interactions, low educational status, overdose, and deficiency in medication counseling either to patients or relatives can increase the chance of regorafenib complications. Therefore, healthcare practitioners, patients, and patients' relatives share equal responsibilities in evaluating the therapeutic state and awareness of regorafenib toxicity [3, 4].

The dosing strategy of Regorafenib has improved recently to provide the maximum efficacy needed with the lower possible side effects. Mainly, there are two dosing strategies, a standard dose which is (160mg/day) for 21 days each cycle, and escalating dose strategy that starts with (80mg/day) with weekly escalation with 40mg if no evidence of side effects [5]. Emphasizing appropriate monitoring and instructing healthcare providers may result in better outcomes and improve the quality of life for patients. However, this requires adherence to the treatment to prevent further drug toxicity. Factors associated with regorafenib adherence and its toxicity are highly diverse among patients. Therefore, it is very important to select patients on an individual basis who can tolerate and benefit from the use of this drug [6].

Regorafenib has a small molecular weight that inhibits multiple membrane-bound and is involved in intracellular kinases of the regular cellular function and pathogenic processes [7]. The FDA has approved regorafenib to be administered to patients with metastatic colorectal cancer (mCRC) [8, 9].

Demetri *et al*. conducted a phase III trial at 57 hospitals in 17 countries in order to evaluate the safety and efficacy of regorafenib on the metastatic form of GISTs. Patients received either a 160 mg dose of regorafenib (as per protocol) or a placebo plus the best supportive care. The primary endpoint was progression-free survival (PFS). They concluded that regorafenib was significantly more effective than placebo in achieving the primary endpoint. However, adverse drug reactions were reported in 130 out of 133 (98%) patients who received regorafenib. Nevertheless, hypertension was the most commonly reported grade 3 adverse reaction which is followed by hand-foot skin reaction and diarrhea [10].

Grothey and coworkers conducted a phase III trial at 114 centers in 16 countries to evaluate the safety of regorafenib in colorectal cancer patients. Patients were divided into a 2:1 ratio to receive regorafenib 160 mg or placebo and the best supportive care for the first 3 weeks cycle followed by 1 week off. The main endpoint was overall survival. They found that regorafenib-related adverse reactions were seen in 465 out of 500 patients. Out of these the most common grade, 3 adverse reactions were hand and foot skin reaction (83 patients, 17%) and fatigue (48 patients, 10%). Regardless of the safety profile of regorafenib, the study provides evidence for continuing regorafenib after disease progression in the treatment-refractory population [11].

Duffaud and coauthors conducted a non-comparative, randomized, double-blind, placebo-controlled study on adult patients with metastatic osteosarcoma disease to evaluate the safety and efficacy profile of regorafenib. The study enrolled 43 patients at 13 different cancer centers in France. Patients were randomly assigned in a 2:1 ratio to receive regorafenib 160 mg once daily for 3 weeks followed by a 1 week off versus placebo with the best supportive care in the interest to reach the primary endpoint, which was the proportion of patients without disease progression at 8 weeks. Nevertheless, 13 patients out of 29 developed serious adverse drug reactions, the most common ones were hypertension (24%) and hand-foot reaction (10%). Clinically, this study shows a significant antitumor activity of regorafenib in recurrent, progressive, and metastatic osteosarcoma [12].

Dane and co-researchers conducted a phase III trial to evaluate the safety and efficacy of regorafenib in patients with colorectal cancer at 11 centers in Turkey. This study enrolled 139 patients. However, only 100 patients were treated and completed the study. In this study, patients received 160 mg of regorafenib for 3 weeks followed by 1 week off until disease progression, which was marked by death or unacceptable toxicity. However, the primary endpoint of this study was safety and progression-free survival (PFS). They reported that 77% of patients developed grade 3 adverse drug reactions. The most commonly reported adverse drug reactions were hypophosphatemia (11%), fatigue (8%), and hyperbilirubinemia (6%). The highlighted result of this study was the regorafenib safety and efficacy profile which makes the medication an option for patients with refractory mCRC in Turkey [13]. This study aimed to evaluate the safety profile of regorafenib and the management of its side effects at King Abdullah Medical City (KAMC) in Makkah, Saudi Arabia.

MATERIALS AND METHODS

This study was a chart review study done at King Abdullah Medical City between December 2021 and May 2020. The files of the patients who received the drug for any indication were consulted for the data extraction.

Inclusion criteria

All patients who received regorafenib at King Abdullah Medical City were included in the study.

Sample size calculation

Since all patients who received regorafenib in the hospital were included in the study, sample size determination was not applied.

Data collection form

A data collection form was designed in an excel sheet, and recorded the following information; MRN, demographic characteristics (age, gender), diagnosis, Regorafenib starting dose, and reported adverse effects. All the data was collected in an excel file that was password-protected. The excel file was dealt with as confidential and was only accessible by the researchers. The adverse effects were reported using the Naranjo scale [14]. The date when the adverse effects were reported, the dose at the time of reporting the adverse effects, the patient status at the time of reporting the adverse effects, and the action taken in response to the occurrence of adverse effects (i.e. dose delay, dose reduction, discontinuation, or none) and the reason for the treatment termination all were reported.

Ethical statement

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of KAMC (IRB number: 21-859). Waiver of informed consent was requested and accepted by the IRB because it was a retrospective chart review study. It was a self-funded study.

Data analysis

The data were analyzed using SPSS software version 25 (IBM SPSS Statistics for Windows, version 25, IBM Corp., Armonk, N.Y., USA). Qualitative data were presented mainly as frequencies and percentages. It was planned to present any association of adverse effects with demographic characteristics using the chi-square; however, due to the variability in the adverse effects, it was not possible to statistically determine their association with the demographics or any other variable using the chi-square test. Therefore, the results are presented as frequencies only. Data were visualized using simple, multiple, and component bar charts.

RESULTS AND DISCUSSION

Due to the variability in the adverse effects, it was not possible to statistically determine their association with the demographics or any other variable using the chi-square test. Therefore, the results are presented as frequencies only.

Demographics and diagnoses

Forty-two patients were found to be on regorafenib. The average age of the patients was 56 years (ranging from 38 to 73 years) of which 12 were females and 30 were males. The majority of the patients received the drug for metastatic colon cancer (28, 66.6%).

Doses received

The number of patients receiving different doses with respect to their diagnosis was shown in **(Table 1)**. The dose of regorafenib that the patients received ranged from 40 mg to 160 mg. In addition, around 55% of the patients were on 80 mg of regorafenib.

Table 1. Number of patients and the received doses in relation to their diagnoses

Dose	Number of patients	Diagnosis	Percentage
40 mg	12	2 with metastatic cecal colonic cancer 10 with metastatic colon cancer	28.57%
80 mg	23	2 with GIST 14 with metastatic colon cancer	54.76%

		6 with metastatic rectal cancer 1 with metastatic rectosigmoid cancer	
120 mg	2	1 with metastatic colon cancer 1 with metastatic sigmoid cancer	4.76%
160 mg	5	1 with metastatic cecal colonic cancer 3 with metastatic colon cancer 1 with hepatocellular carcinoma	11.9%

The majority of total patients (n=42) experienced the adverse effects at the same dose on which they were started. Their details are presented in **(Table 2)**.

A chi-square test was performed using SPSS version 26 and a significant association between doses and diagnosis was found in relation to the adverse effects ($p < 0.001$). Patients with metastatic rectal cancer on 80 mg doses were found to have significantly more adverse effects, followed by metastatic colon cancer on 40 mg and 80 mg doses.

Table 2. The adverse effects reported concerning the diagnoses and doses

Diagnosis	Dose	Adverse effects
Metastatic cecal colonic cancer	40 mg	Shortness of breath and right-sided headache, Fatigue and bone pain, Hyperbilirubinemia, increase in liver enzyme
Metastatic colon cancer	40 mg	Hyperbilirubinemia, Hand and feet syndrome, HFS, nausea, and vomiting, Severe lower abdominal pain, Oral candida, dysphagia, dehydration, Fatigue, elevation in liver enzyme
GIST	80 mg	Generalized aching, epigastric pain, fatigue, vomiting, anemia
Metastatic colon cancer	80 mg	Rectal hemorrhage, Fatigue, HFS, Hyperbilirubinemia, Muscle sprain, epigastric pain, nausea and vomiting, dysphasia, jaundice, increase in liver enzyme, HTN, generalized pain, elevated INR, bleeding, elevated serum creatinine, Palpitation, dehydration, Fever, uncontrolled abdominal pain, constipation, Hypomagnesemia, Bilateral moderate hydronephrosis, the elevation of INR and PT, hand, and feet syndrome, Tachycardia, Dyspnea,
Metastatic rectal cancer	80 mg	Fatigue, muscle aches, Low back pain, lower limb weakness, Drug-induced immune hemolytic anemia, Bilateral moderate hydronephrosis, Multiple spinal compression, fracture, Mild elevation in INR, hyperbilirubinemia, increase in liver enzyme, Epigastric pain, nausea,
Metastatic sigmoid cancer	120 mg	HTN, Hyperbilirubinemia
Hepatocellular carcinoma	160 mg	HTN, Hyperbilirubinemia, mild elevation of INR, Hand ulcers, mouth ulcers, hoarseness of voice, genital ulcer
Metastatic cecal colonic cancer	160 mg	Bleeding, hydronephrosis, elevated INR, epigastric pain, fatigue, liver enzyme
Metastatic colon cancer	160 mg	Nausea, vomiting (severe), Fatigue, hyperbilirubinemia, epigastric pain, the elevation of INR, increase in liver enzymes, bleeding

Dose escalations and the occurrence of adverse effects

Three patients with metastatic cecal colonic cancer experienced side effects when the dose was increased from 40 mg to 80 mg. Increasing the dose from 40 mg to 160 mg was associated with side effects in six patients with metastatic colon cancer and one patient with metastatic cecal colonic cancer. Five patients with metastatic rectal cancer and five patients with metastatic rectosigmoid cancer experienced side effects when the dose was increased from 80 mg to 120 mg. In metastatic colon cancer, side effects were reported in 8 patients when the dose was increased from 80 mg to 160 mg. One patient with metastatic sigmoid cancer experienced the side effects (fatigue, general bone aches) when the dose was increased from 120 mg to 160 mg after 5 months and 12 days **(Figure 1)**.

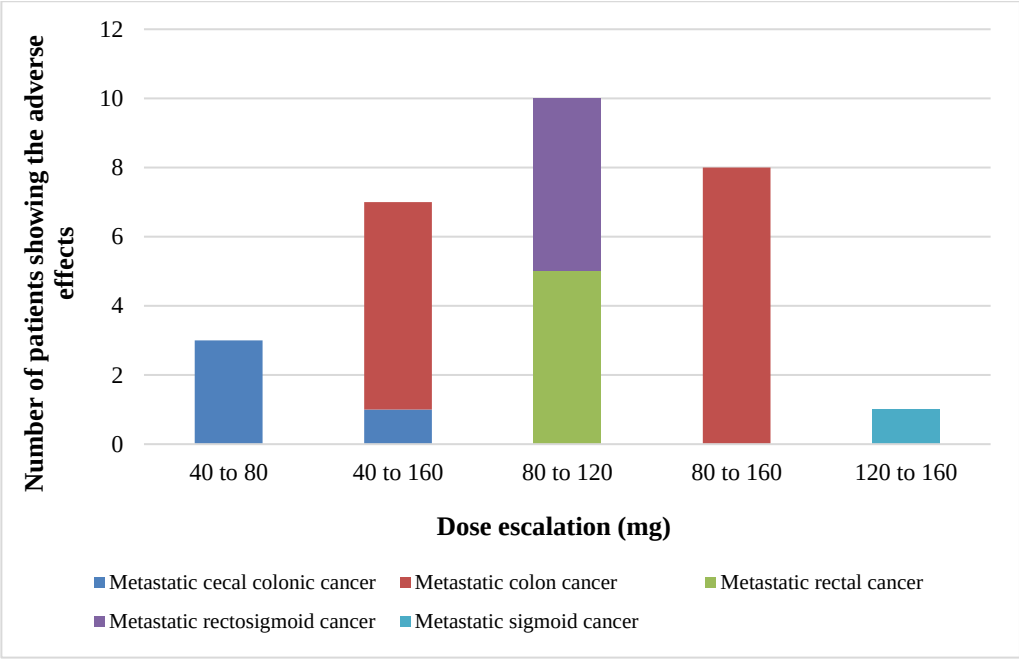

Figure 1. Dose escalation and the occurrence of adverse effects

Patient status at the time of occurrence of adverse effects and the management

Twenty episodes of adverse effects were reported to be stable ('stable' implies the patients who received regorafenib and were exposed to an adverse drug reaction with no intervention needed). Three patients had their dose increased from 40 mg to 80 mg and had the dose reduced later on. Two patients had the dose increased from 40 mg to 160 mg, but it did not result in any change in the management. Two patients had the dose increased from 80 mg to 120 mg and three had the dose increased from 80 mg to 160 mg. The rest of these patients were on the same dose (on which they were started) at the time of occurrence of adverse effects.

Twenty-six episodes of adverse effects were reported to be stable with intervention ('stable with intervention' implies the patients who received regorafenib and were exposed to an adverse drug reaction and required an intervention to be stable). Two patients had their dose increased from 80 mg to 120 mg which resulted in dose delay. One patient had the dose increased from 120 mg to 160 mg, however, it did not lead to any change in the management. The rest of these patients were on the same dose (on which they were started) at the time of occurrence of adverse effects.

Three episodes of adverse effects were reported to be 'not stable' ('not stable' implies the patients who received regorafenib and were exposed to an adverse drug reaction were not stable even with intervention. The details are presented in **Table 3**.

Thirty-one episodes of adverse effects were reported to be 'no tolerance. Five of them had their dose increased from 40 mg to 160 mg, six had their dose increased from 80 mg to 120 mg, and three had their dose increased from 80 mg to 160 mg. The rest of these patients were on the same dose (on which they were started) at the time of occurrence of adverse effects. The details are presented in **(Tables 3 and 4)**.

Table 3. Adverse effects management of the patients

Number of patients	Diagnosis	Dose at the time of reporting adverse effects	Action	End-of-treatment reason
2	Metastatic cecal colonic cancer	160mg	None	
2	Metastatic colon cancer	40mg	None	
2	Metastatic colon cancer	80mg	Dose reduction	
3	Metastatic colon cancer	80mg	None	
2	Metastatic colon cancer	120mg	1P Discontinue 1P None	Poor tolerance
3	Metastatic colon cancer	160mg	1P Dose reduction 2P None	

3	Metastatic colon cancer	80mg	Discontinue	Disease Progression
1	Metastatic rectosigmoid cancer	80mg	None	
2	Metastatic colon cancer	160mg	1P Discontinue 1P None	Poor tolerance
6	Metastatic colon cancer	40mg	None	
9	Metastatic colon cancer	80mg	Discontinue	3p Poor tolerance 1p Disease Progression 3p Disease Progression and Poor Tolerance 2p Bleed
5	Metastatic rectosigmoid cancer	80mg	2p Dose delay 3p None	
2	Metastatic colon cancer	80mg	None	
2	Metastatic colon cancer	120mg	Dose delay	
1	Metastatic sigmoid cancer	160mg	None	
2	Metastatic sigmoid cancer	120mg	Dose reduction	
4	Hepatocellular carcinoma	160mg	Discontinue	Poor tolerance
1	Metastatic rectal cancer	80mg	Discontinue	Poor tolerance
2	Metastatic rectal cancer	160mg	None	

Table 4. Adverse effects management of the patients whose status was recorded as 'no tolerance'

Number of patients	Starting dose	Dose at the time of reporting adverse effects	Action	End-of-treatment reason
1	40mg	40mg	Discontinue	Disease Progression, Poor Tolerance
5	40mg	160mg	Discontinue	Disease Progression
2	80mg	160mg	Dose reduction	
3	80mg	80mg	Discontinue	Not tolerated
3	80mg	80mg	Discontinue	2p Disease Progression, Poor Tolerance 1p Not tolerated
	80mg	80mg	Discontinue	Disease Progression, Poor Tolerance
3	80mg	80mg	Discontinue	2p Disease Progression, Poor Tolerance 1p High risk of bleed
6	80mg	120mg	2p Dose reduction 4p Discontinue	Disease Progression, Poor Tolerance
2	1p 80mg 1p 160mg	160mg	Discontinue	Disease Progression, Poor Tolerance
4	3p 80mg 1p 120mg	3p 80mg 1p 120mg	Discontinue	High risk of bleed

Adverse events reported

The main adverse drug reaction found in our population was hyperbilirubinemia [26 out of 42 patients (61.9%)]. Half of the patients suffered from varying severity of fatigue [21 out of 42 patients (50%)]. Less than half of the patients were found to have high liver enzymes [19 out of 24 patients (45.2%)], and a similar proportion of patients were reported to have a varying degree of INR [19 out of 42 patients (45.2%)], however, only 7 of them had bleeding incidence. Nausea and vomiting were reported in 13 out of 42 patients (30.95%). The pain was found in 12 out of 42 patients (28%) in muscles, bone, or generalized pain. Hands and feet syndrome was found in 5 out of 42 patients (11.9%). Four out of 42 patients (9.5%) were found to have regorafenib-induced hemolytic anemia. Hypertension was developed in 4 out of 42 patients (9.5%). Three out of 42 patients (7.1%) had fractures. New adverse drug reactions were discovered in our population, and not reported in the previous studies were hemifacial spasm (HFS) which was found in 5 out of 42 patients (11.9%) and bilateral hydronephrosis which was found in 3 out of 42 patients (7.14%) **(Figure 2)**.

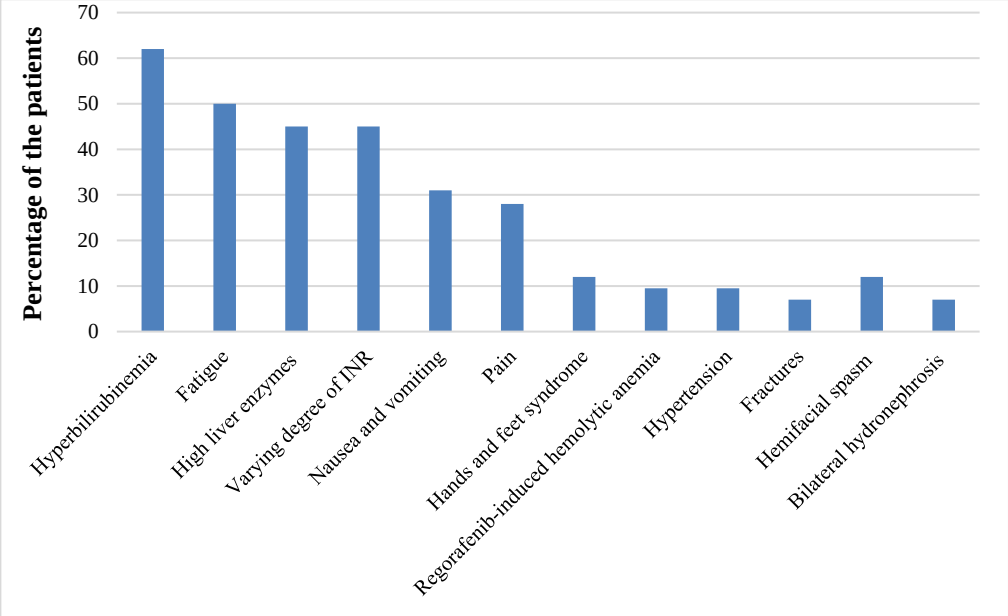

Figure 2. Adverse events reported

Patient management

We found that 22 out of 42 patients discontinued regorafenib generally because of poor tolerance. Eleven patients out of the 22 (50%) switched to another antineoplastic agent, and 11 out of 22 patients (50%) signed for the Do Not Resuscitate Form (DNR) due to disease progression. Furthermore, we found that 12 out of 42 patients (28%) who suffered from adverse drug reactions were stabilized by intervention, 5 out of 12 patients (41.6%) were managed by dose reduction and best supportive care, 2 out of 42 patients (16.6%) were managed by dose delay and best supportive care and 5 out of 12 patients (41.6%) patients were managed by only best supportive care.

In our study, we focused on evaluating the safety of regorafenib in the local Arab population at King Abdullah Medical City. To date, there is no study conducted in the Middle East region regarding the safety profile of regorafenib. Therefore, we do not have any regorafenib safety data available for the population in this region. Furthermore, regorafenib is considered a new chemotherapy medication that has very recently been approved by the FDA to be used in the metastatic phase of various cancers. Currently, adverse events of regorafenib are not well known to healthcare providers, therefore, managing them is a critical step to keep the medication more tolerated by patients. This necessitates the investigation of adverse events of regorafenib in our clinical settings. Since the goal of any cancer center is to improve the quality of life and reduce the mortality rate, King Abdullah Medical City approved the medication in 2015 to be used in the hospital for different types of cancers: colon cancer, rectal cancer, hepatocellular cancer, and sigmoid cancer.

A well-fitted data collection Excel sheet was created that included the patient's demographic, starting dose of regorafenib, type and time of the adverse event, patient status, and primary management. The aim was to evaluate regorafenib from a safety perspective in our local population so as to determine the toxic window of the medication for our healthcare providers. The initial diagnosis of the patient was also included in the data collection to detect any relation between diagnosis and the toxic profile of regorafenib. The adverse events of regorafenib were reported as per the Naranjo scale for both standard and escalation dose strategies. The adverse events were collected from different hospital departments, some were reported from emergency, and others were reported from regular OPD clinics and inpatient oncology wards. Furthermore, all dose adjustments of regorafenib and management of regorafenib-related side effects were reported for evaluation. Moreover, since tolerance plays a critical role in any antineoplastic medication, we also ensured to report the status of the patients as regards tolerance.

As evident from the demographics of the patients in the result, all 42 patients were started on regorafenib in the progression phases (late phase) of their cancers. However, 28 out of 42 patients (66.6%) were found to be diagnosed with metastatic colon cancer which has been recognized as one of the most common cancers in our region [15]. This cancer is also one of the approved indications of regorafenib by the FDA. In our sample, we found that there was no distinct dose strategy followed, the patients were started on varying doses such as 40mg, 80mg, 120mg, and 160mg with no criteria followed. There was no relation found with the diagnosis, however,

the dose choice could have been driven by tolerance of previous antineoplastic medications or the general health status of the patient. In contrast, the regorafenib dose received by the patients in Demetri *et al*. study and Grothey *et al*. study was 160mg [10, 11, 16].

The main adverse event reported in our population was hyperbilirubinemia. In contrast, the main adverse event reported in Demetri *et al*. study and Duffaud *et al*. study was hypertension and in Grothey *et al*. study was hands and feet syndrome [10-12]. The main adverse event reported in Dane *et al*. study was hypophosphatemia. Hyperbilirubinemia was reported by Dane *et al*. study but was only in 6% of the study sample as compared to 62% in our study [13].

Hand-foot skin reaction was reported by Demetri *et al*. (12%), Grothey *et al*. (17%), and Duffaud *et al*. (10%) [10-12]. In our study, it was found in a similar proportion of patients (12%). In contrast, fatigue was reported by Grothey *et al*. (10%) and Dane *et al*. (11%) only [11, 13, 17], However, in our study sample it was reported in 28% of the patients.

One of the limitations of our study is that it presents the data from one healthcare institution only, therefore, it may not be generalizable to the entire Middle East Arab region. Another limitation is that due to variability in the reported adverse events, we could not perform any statistical test. Larger scale multi-institutional studies are warranted to determine any associations between the adverse events and other variables statistically.

CONCLUSION

Regorafenib as evidenced by the published studies and the findings of our study is found to be effective in the management of advanced cancers in our local population. However, it is found to be associated with a variety of adverse events. In the current study, the most common adverse event was hyperbilirubinemia which is followed by fatigue. These findings are in agreement with the reported adverse events in the relevant published literature. From the evidence of the present study, hemifacial spasm and bilateral hydronephrosis were found to be the new adverse drug reactions, which were not reported in other studies. In addition, half of the patients were found to have discontinued the medication due to adverse events.

This study recommended that Regorafenib should be used for the FDA-approved indications or the indications underpinned by the published literature. Regorafenib should be used with an appropriate dose regimen as per the protocol. The treatment with regorafenib should be monitored for safety, efficacy, and tolerability. In the event of adverse events, regorafenib should only be continued, with possible dose modifications, if the benefit outweighs the risk. If the patients cannot tolerate regorafenib, discontinuation should be considered following a careful clinical judgment by the oncologist, with alternative chemotherapy. Since regorafenib is still relatively a new drug, any new adverse events related to regorafenib treatment (not reported in the literature) should be reported to the Saudi FDA.

ACKNOWLEDGMENTS : None

CONFLICT OF INTEREST : None

FINANCIAL SUPPORT : None

ETHICS STATEMENT : None

REFERENCES

1. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.
2. Zhang Q, Wang Z, Wu J, Zhou Z, Zhou R, Hu W. Bioequivalence and pharmacokinetic evaluation of two oral formulations of regorafenib: An open-label, randomised, single-dose, two-period, two-way crossover clinical trial in healthy Chinese volunteers under fasting and fed conditions. Drug Des Devel Ther. 2021;15:3277.
3. Taguchi D, Inoue M, Fukuda K, Yoshida T, Shimazu K, Fujita K, et al. Therapeutic drug monitoring of regorafenib and its metabolite M5 can predict treatment efficacy and the occurrence of skin toxicities. Int J Clin Oncol. 2020;25(4):531-40.

4. Arikawe O, Morrissey H, Ball P. Community pharmacy brief screening intervention to improve health outcomes for patients diagnosed with chronic diseases. J Adv Pharm Educ Res. 2022;12(3):1-8.
5. Mross K, Frost A, Steinbild S, Hedbom S, Büchert M, Fasol U, et al. A Phase I Dose–Escalation Study of Regorafenib (BAY 73–4506), an Inhibitor of Oncogenic, Angiogenic, and Stromal Kinases, in Patients with Advanced Solid TumorsRegorafenib Treatment in Patients with Advanced Solid Tumors. Clin Cancer Res. 2012;18(9):2658-67.
6. Cremolini C, Schirripa M, Loupakis F, Falcone A. Oral multikinase inhibitor regorafenib for the treatment of patients with metastatic colorectal cancer. Colorectal Cancer. 2013;2(5):411-7.
7. Grothey A, Blay JY, Pavlakis N, Yoshino T, Bruix J. Evolving role of regorafenib for the treatment of advanced cancers. Cancer Treat Rev. 2020;86:101993.
8. Modest DP, Pant S, Sartore-Bianchi A. Treatment sequencing in metastatic colorectal cancer. Eur J Cancer. 2019;109:70-83.
9. Alkhayyat S, Khojah M, AlJehan M, Allali D, Tayeb A, Albukhari S, et al. Awareness of Colorectal Cancer in Saudi Arabia: Cross-Sectional Study. Pharmacophore. 2021;12(1):38-43.
10. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.
11. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.
12. Duffaud F, Mir O, Boudou-Rouquette P, Piperno-Neumann S, Penel N, Bompas E, et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol. 2019;20(1):120-33.
13. Dane F, Ozgurdal K, Yalçın Ş, Benekli M, Aykan NF, Yücel İ, et al. Safety and efficacy of regorafenib in patients with treatment-refractory metastatic colorectal cancer in Turkey: the single-arm, open-label REGARD study. BMJ Open. 2020;10(3):e027665.
14. Diseases, B.M.N.I.o.D.a.D.a.K. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. 2012; Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/.
15. Alqahtani WS, Almufareh NA, Domiaty DM, Albasher G, Alduwish MA, Alkhalaf H, et al. Epidemiology of cancer in Saudi Arabia thru 2010–2019: a systematic review with constrained meta-analysis. AIMS Public Health. 2020;7(3):679.
16. Hatori M, Kawakami K, Wakatsuki T, Shinozaki E, Kobayashi K, Aoyama T, et al. Association Between Regorafenib Dose and Efficacy Against Metastatic Colorectal Cancer in a Real-World Setting. Dose Response. 2021;19(4):15593258211047658.
17. Al-Qahtani A, Al-Seeni MN, El-Sherif HA. Potential Effects of Garlic Oil and Curcumin on Carbon Tetrachloride-Induced Liver Injury in Rats. Int J Pharm Phytopharmacol Res. 2020;10(1):155-63.